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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/818,461	03/27/2001	Benjamin D. Silverman	YOR920000779US2	1831

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EXAMINER

BORIN, MICHAEL L

ART UNIT	PAPER NUMBER
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1631

DATE MAILED: 04/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/818,461

Applicant(s)

SILVERMAN, BENJAMIN D.

Examiner

Michael Borin

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 February 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-43 is/are pending in the application.
- 4a) Of the above claim(s) 4,7-21,28-32,36 and 39-43 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3,5,6,22-24,26,27,33-35,37 and 38 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

Appeal Brief filed 02/07/2005 is acknowledged. Upon review of the application additional rejections were deemed necessary. Consequently, the finality of the previous Office action is withdrawn.

Rejections not reiterated from previous Office actions are hereby withdrawn. The following rejections constitute the complete set presently being applied to the instant application. The revised and new grounds of rejections are identified as "revised" and "new", respectively.

Status of the claims

Claims 1-43 are pending. Claims 4,7-21,28-32,36,39-43 remain withdrawn from consideration.

Claim Rejections - 35 USC § 112, second paragraph.

2. Claims 1-3,5,6,22-24,26,27,33-35,37,38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. (new) Claim 1 (claims dependent therefrom) is indefinite due to the lack of clarity of the claim language failing to recite a final process step, which agrees back with the preamble. The preamble states that it is "a method for spatially profiling proteins", however, the claim recites a final step of "shifting the hydrophobicity distribution". While minor details are not required in method/process claims, at least the basic step must be recited in a positive, active fashion. The claim does not set forth the conditions when the determining/shifting of hydrophobicity distribution results in "spatially profiling

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proteins". Also, the preamble addresses spatially profiling plurality of proteins while the main body of the claim addresses a single protein.

B.(revised) Claims 1,22,33, and claims dependent therefrom, recite the step of determining "hydrophobicity distribution of a protein", which is vague and indefinite.

It is not clear, first, whether the distribution of protein addressed in the claim is in some physical environment, virtual environment, or, as it seems from the specification, is not a distribution of protein at all, but distribution of values of hydrophobicity throughout the given protein molecule. Clarification of the language is important as it will define the scope of applicable prior art.

Applicant explains that the hydrophobicity distribution is determined from the spatial distribution of amino acid residues. This may explain the term hydrophobicity distribution of amino acid residues in protein, but not the "hydrophobicity distribution of a protein" as used in the claims. Further, the section in specification addressed by applicant, describes values of hydrophobicity of amino acid residues lying within certain surface, not "hydrophobicity distribution of a protein".

Note, that the term "hydrophobicity distribution of a protein" is not used in prior art with the meaning intended by applicant, and that the applicant himself describing the same subject matter in a subsequent publication uses terms "distribution of amino acid hydrophobicity", "amino acid distribution of hydrophobicity", but never utilizes the ambiguous term "hydrophobicity distribution of a protein" used in this claim language.

See Silverman, D., Proc Natl Acad Sci U S A. 2001 April 24; 98(9): 4996-5001.

Further, even only the limited "*in silico*" meaning of the term intended by applicant is addressed, it is still unclear whether the term "hydrophobicity distribution of a protein" encompasses distribution of hydrophobicity values of individual residues throughout the protein, distribution of hydrophobicity on the surface (or in the core) of the protein, or general vector/matrix indicating distribution of hydrophobicity.

Claim Rejections - 35 U.S.C. § 101

3.(revised) Claims 1-3,5,6 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1-3,5,6 are directed to a computer-implemented method of "spatially profiling proteins" which comprises only computational steps. It is noted that the claims recite ONLY steps of mathematical manipulation of data.

According to MPEP 2106.IV.B.1 :

"If the "acts" of a claimed process manipulate only numbers, abstract concepts or ideas, or signals representing any of the foregoing, the acts are not being applied to appropriate subject matter. Schrader, 22 F.3d at 294-95, 30 USPQ2d at 1458-59. Thus, a process consisting solely of mathematical operations, i.e., converting one set of numbers into another set of numbers, does not manipulate appropriate subject matter and thus cannot constitute a statutory process. In practical terms, claims define nonstatutory processes if they:

- consist solely of mathematical operations without some claimed practical application (i.e., executing a "mathematical algorithm; or
- simply manipulate abstract ideas, e.g., a bid (Schrader, 22 F.3d at 293-94, 30 USPQ2d at 1458-59) or a bubble hierarchy (Warmerdam, 33 F.3d at 1360, 31USPQ2d at 1759), without some claimed practical application. Cf. Alappat, 33 F.3d at 1543 n.19, 31 USPQ2d at 1556 n.19..."

The MPEP, at 2106, also states that claims may be statutory where the claimed invention as a whole, accomplishes a practical application. "That is, it must produce a

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"useful, concrete and tangible result." State Street, 149 F.3d at 1373, 47 USPQ2d at 1601-02. The claims do not recite a "result" of any kind such that the claimed method steps accomplish a practical application. The invention as claimed is drawn to a series of computational steps towards modifying hydrophobicity values of amino acid constituents of a protein in a modeled virtual environment. The specification discloses mathematical steps used in the method. These steps result in a protein model having zero net hydrophobicity in the virtual environment. A process consisting solely of mathematical operates, i.e., converting one set of numbers into another set of numbers, does not manipulate appropriate subject matter and thus can not constitute a statutory process. There is no "useful, concrete, and tangible result" obtained as a result of the claimed method. Applicant states that the "shifted hydrophobicity distribution" may be used for comparing "hydrophobic ratios", but no "useful, concrete, and tangible result" for said "ratios" is identified either.

Claim Rejections - 35 USC § 112, first paragraph.

4. (revised) Claims 1-3,5,6,22-24,26,27,33-35,37,38 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for a computer-driven computational method made on a protein modeled in virtual environment, does not reasonably provide enablement for a method of profiling proteins by physically changing protein's hydrophobicity in a real environment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification appears to disclose a computer program product and computer-implemented method wherein hydrophobicity of amino acid residues comprising the protein of interest are shifted by subtracting the average hydrophobicity from each value of hydrophobicity distribution of each amino acid residue, so that as a result the net hydrophobicity of protein vanishes. The specification appears to indicate that applicant's inventive concept revolves around such specific "shifting" operation, rather than encompasses any broad definition of the term "shifting". This is not reflected in the claims. It is noted that the claims are not limited to well-understood computational and/or physico-chemical processes, and the specification does not provide exemplification or guidance on performing method steps in the broad scope they encompass (e.g., determining hydrophobicity of protein in physical, e.g., aqueous, environment, and shifting the hydrophobicity by physical methods). The specification does not appear to disclose suitable algorithms or implementations. There is no evidence of record that implementation of any of these tasks would have been well known or routinely performed by those of ordinary skill in the art at the time of the invention.

In view of the above, it is the Examiners position that with the insufficient guidance and working examples and in view of unpredictability and the state of art one skilled in the art could not make and/or use the invention with the claimed breadth without an undue amount of experimentation.

Applicant argues that MPEP, in 2164.08, requires that "claims are to be given their broadest reasonable interpretation that is consistent with the specification". The next paragraph of this section of MPEP continues, however, that "If a reasonable interpretation of the claim is broader than the description in the specification, it is

necessary for the examiner to make sure the full scope of the claim is enabled.

Limitations and examples in the specification do not generally limit what is covered by the claims". In the instant case, Examiner considers that interpretation of the claims is broader than the description in the specification, and thus applies the scope of enablement rejection.

Further, applicant asserts that it is not possible to contemplate physically shifting the hydrophobicity distribution of a protein. Examiner disagrees. Merely changing the environment around a protein or modifying surface properties of a protein might lead to redistribution of hydrophobicity of a protein. This is exemplified by the following art rejection over Bar-Or.

Claim Rejections - 35 USC § 102 .

5. (revised) Claim 1 is rejected under 35 U.S.C. 102(b) as anticipated by Bar-Or et al (Database CaPlus, DN 103:84898. Archives of Microbiology, 1985, 142(1), pages 21-27).

Instant claim is drawn to method of spatially profiling proteins comprising steps of determining hydrophobicity distribution of a protein and shifting the hydrophobicity distribution.

Bar-Or et al teach method of modulation of cell surface hydrophobicity by treatment of cell surface proteins with proteolytic agents and/or mechanical shearing, or amphenicol. The method includes initial evaluation of hydrophobicity, which reads on instantly claimed step of "determining a hydrophobicity distribution" , and a step of

treatment of cell surface which clearly shifts hydrophobicity distribution of a protein (e.g., as a result of treatment with a proteolytic agent).

It is the Examiners position that all the elements of Applicant's invention with respect to the specified claim are instantly disclosed by the teaching of the reference cited above.

Applicant argues that the reference is different as it teaches changing cell-surface properties. However, as addressed in the previous rejection, Examiner interprets the claim as encompassing physical, not only computer-generated, changes in hydrophobicity. To this end, the referenced method includes initial evaluation of hydrophobicity, which reads on instantly claimed step of "determining a hydrophobicity distribution", and a step of treatment of cell surface which clearly shifts hydrophobicity distribution of a protein (e.g., as a result of treatment with a proteolytic agent).

5.(new) Claim 1 is rejected under 35 U.S.C. 102(b) as anticipated by Cornette et al. (J. Mol. Biol., 1987,195,659-685).

Instant claim is drawn to method of spatially profiling proteins comprising steps of determining hydrophobicity distribution of a protein and shifting the hydrophobicity distribution.

Cornette teaches calculation of hydrophobic moment for each residue (i.e., determining "hydrophobicity distribution") and plotting them on a graph. For comparative purposes, to compare different approaches, the hydrophobicity values are normalized to have a value of 1000 at the frequency angle of 100° (i.e., "hydrophobicity distribution" is "shifted"). With respect to claims 22,33, the method of Cornette is computer-assisted and thus involves computer medium and computer system.

It is the Examiners position that all the elements of Applicant's invention with respect to the specified claim are instantly disclosed by the teaching of the reference cited above.

Specification

The specification is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. See, page 17. Applicant is requested to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01(b).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph.D., can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should

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you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

A handwritten signature in black ink, appearing to read 'Michael Borin', is positioned to the left of the printed name.

Michael Borin, Ph.D.
Primary Examiner
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mlb